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Health and Environmental Effects Profile for Methyl Methacrylate

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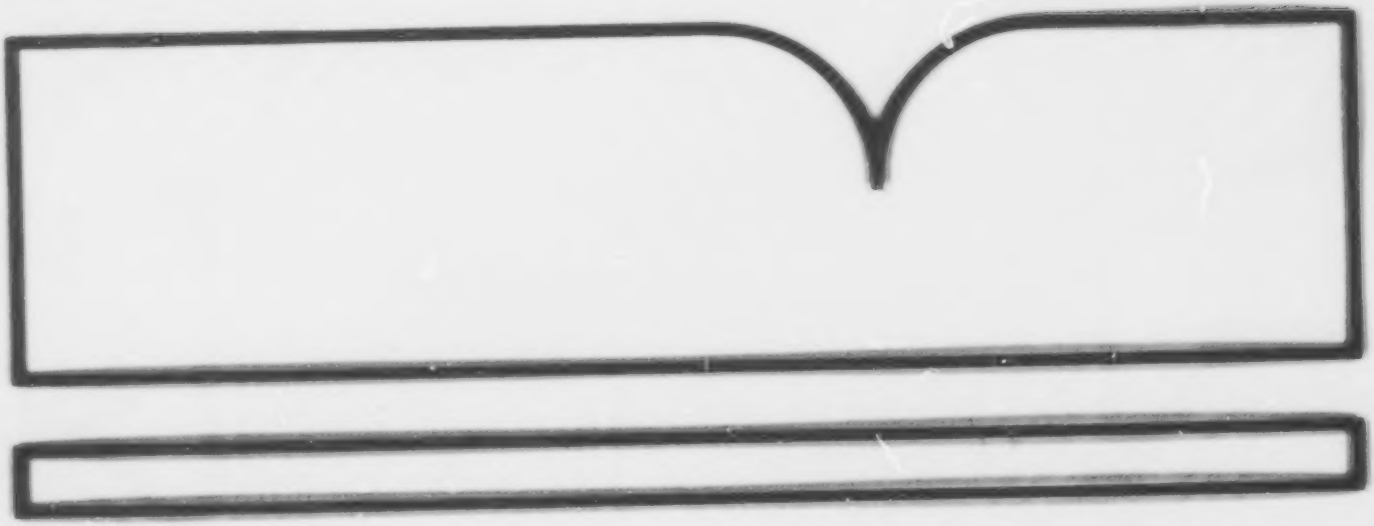

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHYL METHACRYLATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for methyl methacrylate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Methyl methacrylate has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for methyl methacrylate is 5.3 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for methyl methacrylate is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
DMSO	Dimethyl sulfoxide
EC_{50}	Concentration effective to 50% of recipients
ECG	Electrocardiogram
ED_{50}	Effective dose to 50% of recipients
FDA	Food and Drug Administration
GI	Gastrointestinal
GLC-MS	Gas-liquid chromatography - mass spectrometry
i.p.	Intraperitoneal
i.v.	Intravenous
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
LC_{50}	Concentration lethal to 50% of recipients
LT_{50}	Median lethal time
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value

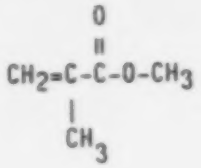
LIST OF ABBREVIATIONS (cont.)

RV_e	Effect-rating value
s.c.	Subcutaneous
SMR	Standardized mortality ratio
STEL	Short-term exposed level
TLV	Threshold limit value
TOTP	Tri-o-tolyl phosphate
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Methyl methacrylate is the common name for 2-methyl-2-propenoic acid, methyl ester. It is also known as methacrylic acid, methyl ester and methyl-2-methyl-propenoate. Some of the common trade names of this compound are MME and Diakon (IARC, 1979; RTECS, 1982). The structure, empirical formula and molecular weight of methyl methacrylate are given below:



The empirical formula for methyl methacrylate is $C_5H_8O_2$ and the molecular weight is 100.1. The CAS Registry number for this compound is 80-62-6.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methyl methacrylate is a colorless volatile liquid at ambient temperature that undergoes ready polymerization by light, heat, ionizing radiation and catalysts (Hawley, 1981). Some of the physical properties of this compound are given below (Nemec and Kirch, 1981, unless otherwise stated).

Melting point:	-48°C
Boiling point at atmospheric pressure:	100-101°C
Density_5^{25}:	0.939 g/mℓ
Flashpoint (Tag open cup):	13°C
Vapor pressure at 20°C:	29.3 mm Hg
Water solubility:	
at 25°C	15,000 mg/ℓ
at 20°C	15,900 mg/ℓ

log K_{ow} (estimated by Fragmentation Method):	0.79	(Lyman et al., 1982)
Conversion factor at 25°C:	1 ppm = 4.09 mg/m³	

Methyl methacrylate undergoes a variety of nucleophilic addition reactions and Diels-Alder reactions. The hydrogen in the allylic methyl group of methyl methacrylate also undergoes substitution reactions with nitro or nitroso groups. The ester moiety of methyl methacrylate is subject to saponification, transesterification and reduction (Nemec and Kirch, 1981).

1.3. PRODUCTION DATA

Several methods have been proposed for the manufacture of methyl methacrylate (Nemec and Kirch, 1981). Currently, the only commercial method used in the United States to manufacture this compound is the acetone cyanohydrin process (SRI, 1984). In this process acetone and hydrogen cyanide are reacted to produce acetone cyanohydrin, which is then treated with concentrated sulfuric acid. The resulting methacrylamide sulfate is reacted with methanol to form methyl methacrylate, which is then purified by distillation. The methyl methacrylate obtained from this process is 99.8% pure. A typical specification of commercial methyl methacrylate available in the United States is as follows: methyl methacrylate, 99.8%; methacrylic acid, 0.003%; water, 0.03%; hydroquinone and monomethyl hydroquinone as inhibitors, 10-15 ppm (IARC, 1979; Nemec and Kirch, 1981).

A proposed two-stage oxidation of isobutylene or t-butyl alcohol to methacrylic acid with its subsequent esterification by methanol to methyl methacrylate is probably the most likely route for the future expansion of the methyl methacrylate industry (Nemec and Kirch, 1981).

The principal United States manufacturers of methyl methacrylate as listed by both USITC (1984) and SRI (1984) are given below:

Manufacturer/Location	Capacity (million pounds/year)
CYRO Industries, Inc., Avondale, PA	200
DuPont Co., Inc., Memphis, TN	240
Rohm and Haas Co., Deer Park, TX	660
Total	1100

The 1983 production of methyl methacrylate in the United States was 844 million pounds. Of this total amount, only 241 million pounds were sold in the merchant market (USITC, 1984); this indicates that the manufacturers used most of their own manufactured product, but not necessarily captively. For example, Rohm and Haas Co. ships methyl methacrylate to its other plants in Bristol, PA, Knoxville, TN and Louisville, KY to manufacture other methacrylate products (SRI, 1984). According to an estimate by Patterson et al. (1976) ~1% of total production or 7.9 million pounds of this compound was emitted in the atmosphere from production, end-product manufacture, and bulk storage in 1974. With proper control technology, the atmospheric emission can be reduced substantially (Patterson et al., 1976).

1.4. USE DATA

The most important use for methyl methacrylate is in the preparation of polymers. The principal uses of this compound in 1978 were as follows (Nemec and Kirch, 1981; TSCA-ITC, 1980): cast sheet and other grades, 43.6% (advertising signs and displays, lighting fixtures, glazing and skylights, building panels and sidings and plumbing and bathroom fixtures); coatings, 18.7% (latex paints, lacquer, enamel resins); molding/extrusion powder, 26.7% (control dials and knobs, instrument cores, wheel discs, directional light covers and lenses for the automobile industry); miscellaneous, 11.1%

(emulsion polymers, polyester modification, transesterification and acrylic fibers). Small amounts of methyl methacrylate were also used in the dental industry as tooth restoration resins, in orthopedic surgery and as various other biomedical materials.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

The fate of methyl methacrylate in the atmosphere has not been comprehensively studied. In a smog chamber study, Joshi et al. (1982) determined the reactivity of methyl methacrylate toward NO_x reactions. At a methyl methacrylate-to-NO_x ratio of 1:2 and 1:20, the half-life of methyl methacrylate was determined to be 2.7 days and >3 days, respectively. At a methacrylate-to-No_x ratio of 1:2, a maximum amount of ozone of 0.73 ppm was formed in 4.4 hours and at a ratio of 1:20, 0.2 ppm were formed in 1.4 hours.

The reactivity of methyl methacrylate toward singlet molecular oxygen ($^1\Delta_g$) was determined to be 1.8×10^{-17} cm^3 $molecule^{-1}$ sec^{-1} (Datta and Rao, 1979). If the concentration of singlet molecular oxygen ($^1\Delta_g$) is assumed to be 2×10^7 molecules cm^{-3} (Graedel, 1978), the half-life for this atmospheric reaction is >60 years. Therefore, this reaction is not significant in determining the fate of methyl methacrylate in the atmosphere.

The direct photolysis of methyl methacrylate in the atmosphere is likely to be significant in determining its fate in the atmosphere. The photolysis of 4 mℓ methyl methacrylate in 2 mℓ dioxane solution at a wavelength >300 nm yielded 0.43% of the polymer in 1.2 hours (Otsu et al., 1979). Unfortunately, no kinetic data are available regarding the vapor phase photolysis of methyl methacrylate in direct or simulated sunlight. It is also likely that ketonic compounds may accelerate the photoreaction of methyl methacrylate in the atmosphere (Otsu et al., 1979).

No information regarding the significance of physical removal rates of methyl methacrylate from the atmosphere is available. Because of its vapor pressure, the removal of this compound through adsorption on aerosols seems

unlikely (Cupitt, 1980). The aqueous solubility of methyl methacrylate is such that some removal of this compound through dissolution into rain droplets is expected.

2.2. WATER

The photolysis of methyl methacrylate in dioxane at wavelength >300 nm produced 0.43% of the polymer in 1.2 hours (Otsu et al., 1979). This shows that this compound may undergo photochemical reaction in the ambient aquatic media. It is difficult, however, to evaluate the significance of this in determining the aquatic fate of methyl methacrylate because of the lack of kinetic data that simulate environmental conditions.

Kinetic data regarding the hydrolysis of methyl methacrylate in aquatic media are not available. Hynkova and Hrabak (1979) conducted a hydrolysis experiment using methyl methacrylate in a 2.5% aqueous alcoholic sodium hydroxide solution, and reported ~80% hydrolysis of ester in 25 minutes. Under more natural environmental conditions, the hydrolysis half-life of ethyl acrylate at pH 7 and 25°C was reported to be 3.5 years (Mabey and Mill, 1978). Therefore, the hydrolysis of methyl methacrylate, a compound structurally similar to ethyl acrylate, may not be significant under ambient aquatic conditions.

The biodegradability of methyl methacrylate under biological treatment conditions was reported by several authors. Thom and Agg (1975) qualitatively reported that methyl methacrylate was biodegradable with acclimatized sewage sludge. Pahren and Bloodgood (1961) reported a 47% theoretical oxidation of methyl methacrylate to CO_2 in 10 days using 19-day acclimatized sewage as microbial inoculum. In an abstract of an investigation, Slave et al. (1974) reported 100% degradation of methyl methacrylate in ~20 hours with activated sludge as the source of mixed microorganisms. It is obvious

from the studies described in this section that methyl methacrylate is likely to undergo significant biodegradation under ambient aquatic conditions; however, no quantitative significance of the biodegradation process can be assigned.

Information on the loss of methyl methacrylate from aquatic media by physical removal processes was not located in the available literature cited in the Appendix. Based on the vapor pressure and solubility data given in Section 1.2., the Henry's constant for this compound is estimated to be 2.4×10^{-4} atm m^3 mol^{-1}. Therefore, it is speculated from the chart of volatility vs. Henry's Law constant (Lyman et al., 1982) that this compound will volatilize significantly from aquatic media. The adsorption coefficient for methyl methacrylate onto sediments in aquatic media is not available. Based on the log K_{ow} value given in Section 1.2. and the correlation equation, Log K_{oc} = 0.544 log K_{ow} + 1.377, by Lyman et al. (1982), a log K_{oc} (K_{oc} adsorption coefficient standardized to percent organic matter content) value of 1.80 is determined. Therefore, this compound may not significantly sorb onto particulate matter in aquatic media.

No experimental value for the BCF for methyl methacrylate in aquatic organisms is available. If the correlation equation, log BCF = 0.85 log K_{ow}-0.7 is used (Veith et al., 1979), the estimated log BCF for this compound is -0.03. Therefore, it is speculated that methyl methacrylate will not bioconcentrate in aquatic organisms.

2.3. SOIL

Pertinent data regarding the fate of methyl methacrylate in soil were not located in the available literature as cited in the Appendix. Based on

the preceding discussions of the fate of this compound in aquatic media, the following speculations have been made regarding its fate in soil:

1. The compound may significantly evaporate from soil surfaces.

2. Appreciable microbial degradation of the compound in soil may be expected.

3. In some instances where the microbial degradation is retarded (accidental spill or dumpsites), methyl methacrylate may leach into groundwater.

3. EXPOSURE

3.1. AIR

The total emission of methyl methacrylate to ambient air in the United States in 1974 from production facilities, end-product manufacturers and storage was estimated to be ~8 million pounds (IARC, 1979). Ambient atmospheric monitoring data for this compound in the United States, however, are not available. In a survey to determine the exposure of workers to airborne contaminants in a polystyrene production plant, Samimi and Falbo (1982) reported the mean TWA concentration of methyl methacrylate in workers' breathing zones and in the air of the workplace as 66 and 169 ppb, respectively. Maximum breathing zone and workplace concentrations of 378 and 3300 ppb, respectively, were reported for methyl methacrylate (Samimi and Falbo, 1982). The 8-hour TWA exposure to methyl methacrylate at five United States plants manufacturing polymethyl methacrylate sheet ranged from 16-360 mg/m^3 (IARC, 1979).

Methyl methacrylate is expected to be present in the air during the drying of acrylic-based paints (IARC, 1979). Methyl methacrylate has also been reported at concentrations below the hygienic TLV in dental work rooms and in surgical rooms when acrylic bone cement is used during hip replacement operations (Vedel and Lausten, 1981; Brune and Beltesbrekke, 1981).

3.2. WATER

Ewing et al. (1977) monitored 204 heavily industrialized river basin sites in the Chicago and Illinois River basin area and reported a methyl methacrylate concentration of 10 ppb in a surface water sample from one site. Of the nine sites monitored in Lake Michigan, Konasewich et al. (1978) also reported a methyl methacrylate concentration of 10 ppb in one water sample.

Methyl methacrylate was detected in a few drinking waters in the United States at a concentration of <1 ppb (Shackelford and Keith, 1976; IARC, 1979). It was also qualitatively detected in a commercial deionized charcoal-filtered water (Dowty et al., 1975).

3.3. FOOD

Under an FDA regulation, methyl methacrylate is permitted to be used as a defoaming agent in the manufacture of paper and paperboard intended for food-contact use (Federal Register, 1982). Plastics made from polymethyl methacrylate may also be used as a food-contact material. Therefore, the possibility of human exposure to methyl methacrylate through the migration of the monomer from the container into foods requires some scrutiny. The extent of migration of the monomer into food from polymethyl methacrylate plastic containers was determined by using food simulating solvents (Inoue et al., 1981). The migration of methyl methacrylate into 20% ethanol at 25°C was 1 ppm in 1 day and 10 ppm in 90 days. The amount of migration into water at 25°C was below the detection limit in 90 days; however, with water heated to 70°C, 2 ppm of the monomer migrated into water in 24 hours (Inoue et al., 1981).

3.4. DERMAL

Weagemaekers et al. (1983) studied the possibility of dermal exposure of methyl methacrylate to orthopaedic surgeons using bone cement containing this material. These authors studied several variations of surgical gloves and found that all the examined materials were unsatisfactory in preventing dermal exposure from bone cement containing methyl methacrylate.

4. PHARMACOKINETICS

4.1. ABSORPTION

Methyl methacrylate is rapidly and extensively absorbed from the GI tract of rats as demonstrated by the experiments of Bratt and Hathway (1977). Adult male Wistar rats were treated with ^{14}C-methyl methacrylate, designated as methyl[1,3-^{14}C]-propylene-2-carboxylate to clearly show the position of the label, at 5.7 mg/kg either by gavage or intravenously. Regardless of the route of administration, ~65% of the administered radioactivity was expired as $^{14}CO_2$ in 2 hours. Recovery of radioactivity over 10 days following the oral dose was 4.7% in urine, 2.7% in feces, 88.0% as $^{14}CO_2$, 0.1% as unchanged ^{14}C-methyl methacrylate in the expired air and 4.1% in carcass and skin for a total recovery of 99.6%. Following the i.v. dose, recovery of radioactivity was 6.6% in urine, 1.7% in feces, 84.0% as $^{14}CO_2$, 0.7% as unchanged ^{14}C-methyl methacrylate in the expired air and 6.6% in the carcass and skin for a total recovery of 99.6%. The nearly identical pattern and amount of recovery of radioactivity following oral dosing and i.v. dosing indicated 100% absorption by the GI tract.

Pertinent data regarding absorption of methyl methacrylate by the respiratory tract were not located in the available literature as cited in the Appendix.

4.2. DISTRIBUTION

McLaughlin et al. (1973) studied the clearance of radioactivity from the blood of beagles (12 kg in weight) following injection into the external jugular vein of ^{14}C-methyl methacrylate administered successively at 45-minute intervals at doses of 25, 50 and 75 mg/kg. Blood was sampled at the femoral artery and inferior vena cava. Peak arterial blood levels of radioactivity of ~4, 30 and 50 mg % were reached in 30 seconds following the 25,

50 and 75 mg/kg doses, respectively, and declined rapidly to ≤2 mg % at 1, 3 and 5 minutes, respectively. The rapid clearance of methyl methacrylate from blood, taken together with the rapid metabolism of methyl methacrylate and excretion of its metabolites (Sections 4.1. and 4.4.) indicate little tendency for accumulation of methyl methacrylate within tissues.

Bratt and Hathway (1977) found that 10 days after oral or i.v. dosing of rats with ^{14}C-methyl methacrylate, radioactivity remained only in the liver and adipose tissue. Consistent with the scheme that methyl methacrylate is metabolized by intermediary metabolism (Section 4.3.), it was suggested that some of the ^{14}C-acetate that would be generated from ^{14}C-methyl methacrylate involvement in the tricarboxylic acid cycle had been incorporated into triglyceride fat.

4.3. METABOLISM

In the previously described study of Bratt and Hathway (1977), adult male rats were given ^{14}C-methyl methacrylate, designated as methyl-[1,3-^{14}C-]-propylene-carboxylate, intravenously or intragastrically at 5.7 mg/kg. Regardless of the route of administration, 84-88% of the dose of radioactivity was found in the expired air as $^{14}CO_2$. Bratt and Hathway (1977) also administered ^{14}C-methyl methacrylate labeled as methyl-[2-^{14}C]-propylene-2-carboxylate intravenously at 5.7 mg/kg. The pattern and amount of recovery of radioactivity was essentially indentical to that following administration of methyl[1,3-^{14}C]-propylene-2-carboxylate, with 84.1% of the dose expired as $^{14}CO_2$. The urinary metabolites included ^{14}C-methacrylic acid, ^{14}C-methylmalonic acid (^{14}C-isosuccinic acid) and ^{14}C-succinic acid. Since equal amounts of $^{14}CO_2$ were expired following administration of ^{14}C-methyl methacrylate, regardless of the position of the label and since urinary metabolites suggested involvement of

components of intermediary metabolism, Bratt and Hathway (1977) proposed that methylmalonyl CoA, formed from methacrylic acid after hydrolysis of methyl methacrylate, is converted enzymatically to succinyl CoA by methylmalonyl mutase. According to the scheme, all four carbon atoms from methacrylic acid enter the tricarboxylic acid cycle simultaneously, accounting for the rapid expiration of identical amounts of $^{14}CO_2$ regardless of the position of the label. Incorporation of ^{14}C-acetate into normal physiologic biochemical molecules such as triglycerides (see Section 4.2.) may occur.

Crout et al. (1979) and Corkill et al. (1976) demonstrated that methyl methacrylate was hydrolyzed enzymatically to methacrylic acid and methanol in human blood in vivo and in vitro.

It was proposed, therefore, that methyl methacrylate is hydrolyzed to methacrylic acid, which is converted into its coenzyne A ester, which in turn enters the tricarboxylic acid cycle. In order to test the proposal, Crout et al. (1982) demonstrated that ^{14}C-methyl methacrylate was directly converted to ^{14}C-methylmalonic acid labeled in the same carbon atom. Two female Wistar rats were treated intraperitoneally with 7 or 9 mg methyl-[Me-^{14}C]methacrylate. Within 10 hours, ~80% of the radioactivity was recovered in the expired air as $^{14}CO_2$, while ~11% (mean of two rats) was recovered in the urine. The ^{14}C-methylmalonic acid in the urine was extracted, converted to the dicyclohexylammonium salt and radioactivity was determined. An average of 0.22% of the administered radioactivity was found. The dicyclohexylammonium salt of methylmalonic acid was oxidized to yield the ^{14}C-acetic acid and the rest of the molecule as CO_2. The ^{14}C-acetic acid contained 95-99% of the radioactivity from the starting ^{14}C-methylmalonic acid, while only 1.5% was $^{14}CO_2$. Thus, Crout et al.

(1982) confirmed the metabolic pathway in rats. To determine if the mechanism also operates in man, Crout et al. (1982) administered sodium-[Me-$^{2}H_{3}$]methacrylate orally to a volunteer and, by an experiment similar to that using rat urine, found direct conversion to [Me-$^{2}H_{3}$]methylmalonic acid.

Delbressine et al. (1981) demonstrated that glutathine conjugation of methyl methacrylate may play a minor role in the metabolism. Following a single i.p. dose of methyl methacrylate (0.14 m/mol/kg) in arachis oil to rats, no significant increase in urinary thioether excretion was detected compared with arachis oil-treated controls. Pretreatment of the rats with TOTP, an inhibitor of carboxylesterase, dramatically increased the excretion of thioether, indicating that if conversion of methyl methacrylate to methacrylic acid is prevented, glutathione conjugation may compete for methyl methacrylate metabolism. Following i.p. treatment of rats with methyl methacrylate at 0.70 mmol/kg/day 5 days/week for 3 weeks, N-acetyl-S-(2-carboxypropyl)cysteine monomethyl ester was identified in the urine.

4.4. EXCRETION

In the previously described study of Bratt and Hathway (1977) (see Sections 4.1. and 4.3.), rats treated orally or intravenously with ^{14}C-methyl methacrylate excreted ~65% of the dose in the expired air as $^{14}CO_{2}$. After 10 days of the oral dose, recovery of radioactivity was 4.7% in the urine, 2.7% in feces, 88.0% as $^{14}CO_{2}$, 0.1% as unchanged ^{14}C-methyl methacrylate in the expired air and 4.1% in the carcass and skin. A similar pattern was found after the i.v. dose and after a much higher oral dose (120 mg/kg), although the higher oral dose was metabolized more slowly Crout et al. (1982) also found ~85% of the administered dose of methyl[Me-^{14}C]-methacrylate as $^{14}CO_{2}$ in the expired air of intraperitoneally treated rats.

McLaughlin et al. (1973) found that radioactivity from ^{14}C-methyl methacrylate was cleared from the blood of dogs within ~5 minutes following an i.v. dose of 75 mg/kg.

5. EFFECTS

5.1. CARCINOGENICITY

A technical report that evaluates the results of a chronic 2-year inhalation exposure to methyl methacrylate in rats and mice is being drafted (NTP, 1985).

Borzelleca et al. (1964) administered methyl methacrylate in drinking water to groups of 25 male and 25 female Wistar rats at concentrations of 0, 6, 60 and 2000 ppm. At the start of the 5th month, the 6 and 60 ppm levels were raised to 7 and 70 ppm, respectively, and treatment was continued for 2 years. No differences in mortality were observed among the groups with 9-18 rats surviving in each group. Histopathologic studies were performed on heart, lung, liver, kidney, urinary bladder, spleen, gastroenteric, skeletal muscle, bone marrow, skin, brain, thyroid, adrenal, pancreas, pituitary and gonads in all rats that died during the study and those that were killed after 2 years except those in the lowest dose group. Histopathologic findings showed no treatment-related abnormalities or lesions.

Hazelton Laboratories America, Inc. (1979a) exposed groups of 56 male and 56 female Golden hamsters by inhalation to methyl methacrylate at concentrations of 0, 25 ppm (102 mg/m^3), 100 ppm (409 mg/m^3) and 400 ppm (1638 mg/m^3) for 6 hours/day, 5 days/week, for 78 weeks. No treatment-related tissue alterations were seen after histopathological examination.

Hazelton Laboratories America, Inc. (1979b) also exposed groups of 70 male and 70 female Fischer rats to concentrations of 0, 25 ppm (102 mg/m^3), 100 ppm (409 mg/m^3), and 400 ppm (1638 mg/m^3) methyl methacrylate vapor in filtered air for 6 hours/day, 5 days/week for 104 weeks. No increased incidence of neoplasm was observed in treated rats compared with controls.

As reviewed by IARC (1979), Oppenheimer et al. (1955) painted 10 Wistar rats on the back of the neck with methyl methacrylate 3 times/week for 4 months and then observed the animals for the remainder of their lifespan. No local tumors were observed.

In a teratogenicity study (Section 5.3.) groups of five pregnant Sprague-Dawley rats were treated intraperitoneally with methyl methacrylate at 0.1328, 0.2656 or 0.4427 mL/kg on days 5, 10 and 15 of gestation (Singh et al., 1972). The dams were killed on day 20 of gestation. The incidence of gross abnormalities of fetuses from the treated females were 1/43 (2.3%) at 0.1328 mL/kg, 4/50 (8.0%) at 0.2656 mL/kg and 8/48 (16.7%) at 0.4427 mL/kg. Only 2/195 control fetuses had gross abnormalities (Section 5.3.). The most common abnormality was hemangiomas, but the specific incidence was not reported.

A retrospective epidemiology study was conducted on male workers employed at a plastics manufacturing plant in Bristol, PA, from January 1933 to December 1945 (Rohm and Haas Co., 1984). The results are summarized in Table 5-1. The total cohort consisted of 3934 white men, who were studied until December 31, 1981. Mortality analyses were performed using the Occupational Cohort Mortality Analysis Program (Marsh and Preininger, 1980). Predicted causes of deaths were calculated from rates for the United States white male population. At the end of the follow-up period, 49% of the cohort were alive, 39% had died and for 12% the vital status was unknown. Observed cancer deaths were 92% of predicted (323 observed, 351.8 predicted; SMR=92). The only cancer SMR that was higher than predicted was cancer of the colon and rectum (52 observed, 31.2 predicted; SMR=167, $p<0.01$).

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TABLE 5-1

Occupation Exposure in Humans to Ethyl Acrylate/Methyl Methacrylate*

Size of Exposed Population	Size of Control Population	Sex	Duration of Exposure (years)	Tumor Type and Site	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value)
3934 exposed and nonexposed	U.S. white male population	M	≤12	malignant cancer of colon, rectum	52	31.2	SMR=167 (p<0.01)
2754 never exposed	U.S. white male population	M	≤12	malignant cancer of colon, rectum	54	29.8	SMR=171 (p<0.01)
<2754 exposed	U.S. white male population	M	≥1-≤12	malignant cancer of colon, rectum	43	20.5	SMR=210 (p<0.01)
1180 never exposed	U.S. white male population	M	NA	malignant cancer of colon, rectum	9	10.7	SMR= 84

QUALITY OF EVIDENCE

Strengths of Study:	Large cohort size, analyses also conducted for estimated accumulated dose and latency (see Section 5.1.), appropriate statistical analyses performed; incidences also compared with regional rates (see Section 5.1.)
Weaknesses of Study:	Could not separate exposure to ethyl acrylate from exposure to methyl methacrylate, no actual exposure levels
Overall Adequacy:	Limited
Comments:	Although a causal relationship was suggested, it could not be established based on analyses broken down for estimated accumulated "dose" and latency (see Section 5.1.)

*Rohm and Haas Co., 1984

NR - Not reported

NA - Not applicable

10/09/85

Similar results were found among employees who had ever been exposed to ethyl acrylate/methyl methacrytale (70% of total cohort or ~2754 men); there were 54 cases of colorectal cancers compared with 29.8 expected (SMR=171, $p<0.001$). When analyzed for employees exposed to ethyl acrylate/methyl methacrylate for at $\geq$1 year (percent of total cohort not reported), 43 cases of colorectal cancer were found, compared with 20.5 predicted (SMR=210, $p<0.01$). In addition, 3 men died of testicular cancer compared with 0.8 predicted (SMR=375), but the incidence of testicular cancer was not considered exposure-related because the types of cancer and work histories of the three men differed. When deaths from colorectal cancer occurring $\geq$10 years after the initial exposure were considered, there were 38 found compared with 18.9 predicted (SMR=201).

For employees who had never been exposed to ethyl acrylate/methyl methacrylate, there were 9 deaths from colorectal cancer compared with 10.7 expected (SMR=84) and 9 deaths compared with 9.6 expected (SMR=93) for $\geq$10-year latency.

Therefore, a causal relationship between exposure and increased relative risk of cancer of the colon and rectum was suggested. No clear relationship, however, between exposure and colorectal cancer could be found in the group exposed for $\geq$1 year to ethyl acrylate/methyl methacrylate when exposures were broken down by estimated accumulated "dose" (determined by ranking the level of exposure for various jobs, assigning a relative index and multiplying by the amount of time spent in the jobs) and when latency (number of years between first exposure and death) was considered. The relative risk was greater for employees with accumulated doses of 1-10 (SMR=213) than for employees with doses >10 (SMR=198). Furthermore, relative risk was greater when latency was <10 years (SMR=377) than when latency

was >20 years (SMR=208), for which the highest ratio of observed to predicted would be expected for colorectal cancer. For workers with the highest exposure indices (not clearly defined but consisting of 47% of the exposed group), 19 deaths from colorectal cancer were found compared with 10.6 predicted (SMR=179); the SMR for the total exposed group was 210.

In an attempt to explain the higher than predicted mortality from colorectal cancer in the total exposed group based on regional differences, the rates for white males in Pennsylvania or New Jersey (areas of higher frequency of colorectal cancer than the United States in general) were used for predicted rates. The observed number of cases still significantly ($p<0.05$) exceeded the predicted number of cases but to a lesser extent. Since a causal relationship between ethyl acrylate/methyl methacrylate exposure and the increased relative risk of cancer of the colon and rectum in workers exposed to the chemicals could not be established by the analyses conducted, further analyses and studies in other plants are now in progress (Rohm and Haas Co., 1984).

5.2. MUTAGENICITY

Mutagenicity studies of methyl methacrylate are summarized in Table 5-2. Barsky (1975), using Salmonella typhimurium strains TA1535, TA1537 and TA1538, found methyl methacrylate to be nonmutagenic with or without S9, in concentrations up to 10 mg/plate.

Anderson (1976a) used S. typhimurium strains TA1535, TA1538, TA98 and TA100 in the reverse mutation assay. Concentrations of vapor methyl methacrylate of 9000 ppm (36,846 mg/m³), 1000 ppm (4094 mg/m³) and 100 ppm (409 mg/m³) in air were used. Concentrations of 2500, 500, 100, 20 and 6 µg/plate were also used in plate incorporation assays. No increases were observed in reverse mutations.

TABLE 5-2

Mutagenicity and Chromosomal Aberrations with Methyl Methacrylate

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA100, TA98	plate incorporation	≤10 mg/plate	±S9	-	Did not test TA100, TA98	Barsky, 1975
		vapor phase	vapor range 409-36,846 mg/m³	NR	-	Did not test TA1537	Anderson, 1976a
		plate incorporation	6-2500 µg/plate	NR	-	Dissolved in DMSO	Anderson 1976a
		plate incorporation or liquid incubation	0-1000 µg/plate	±S9	-	NC	Litjinsky and Andrews, 1980
		plate incorporation or liquid incubation	100-10,000 µg/plate	±S9	-	Liquid incubation with TA100 only	Waegemaekers and Bensink, 1984
		plate incorporation or liquid incubation	NR	NR	-	Did not test TA1535, TA1538	Ishidate et al., 1981
Forward mutation	S. typhimurium TM677	liquid incubation	50-100 mM x 2.0 hours	±S9	±	NC	Poss et al., 1979
Chromosomal aberrations	rat	vapor inhalation	409-36,846 mg/m³	NA	+	Significant differences at 1000 and 9000 ppm	Anderson, 1976b
	hamster	tissue culture of fibroblasts	0.0065 mg/ml	NR	+	NC	Ishidate et al., 1981
Micronucleus test	mouse	NR	NR	NR	-	NC	Hacmiya et al., 1982
Dominant lethal	mouse CD-1	inhalation	409-36,846 mg/m³, 6 hours/day, 5 days	NA	-	NC	Anderson, 1976c

NR = Not reported

NC = No comment

Hacmiya et al. (1982) obtained negative results in the Ames test and mouse bone marrow micronucleus test. No additional information was available. Lijinsky and Andrews (1980), using S. typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, found methyl methacrylate to be nonmutagenic with or without S9 in concentrations up to 1000 µg/plate when tested by plate incorporation or by liquid preincubation.

Waegemaekers and Bensink (1984) found methyl methacrylate to be nonmutagenic in concentrations of 100, 1000 and 10,000 µg/plate with or without S9 in S. typhimurium strains TA100, TA1535, TA1537, TA1538 and TA98 in plate incorporation assays. A negative result was also obtained in TA100 when tested in liquid incubation assay.

Poss et al. (1979) detected methyl methacrylate as a mutagen in a forward bacterial mutation assay, using S. typhimurium strain TM677 in the presence of S9.

Anderson (1976b) investigated the cytogenetics of rat bone marrow after inhalation exposure to concentrations of 100, 1000 and 9000 ppm (409, 4094 and 36,846 mg/m³) for either a single 2-hour exposure or exposure for 5 hours/day for 5 successive days. Significant differences from controls were found at the two higher levels. At 100 ppm, no rat bone marrow abnormalities were observed.

Ishidate et al. (1981) conducted the reverse mutation assay with methylacrylate using S. typhimurium strains TA98, TA100 and TA1537, in conjunction with in vitro chromosomal aberration tests using a Chinese hamster cell line of lung fibroblast origin. The Ames test was negative, but the chromosomal aberration test was positive.

Anderson (1976c) conducted a dominant lethal assay in fertile male CD-1 mice. No increased incidences of pre- or postimplantation loss or early

fetal deaths were detected following mating of female mice with males exposed to inhalation concentrations of 9000, 1000 and 100 ppm (36,846, 4094 and 409 mg/m³) for 6 hours/day for 5 days.

5.3. TERATOGENICITY

As reviewed by TSCA-ITC (1980) and Rohm and Hass Co. (1980), Hodge and Palmer (1977) exposed groups of 30 pregnant rats to concentrations of 0, 100 ppm (409 mg/m³) or 1000 ppm (4094 mg/m³) methyl methacrylate by inhalation for 5 hours/day from days 6-15 of gestation. The experiment was repeated with groups of 30 pregnant rats exposed at 0, 25 ppm (102 mg/m³), 100 and 1000 ppm, 5 hours/day. On day 20 of gestation, the rats were killed and uterine contents examined. No teratogenic effects were observed at any concentration. At 1000 ppm (4094 mg/m³), there was an increased incidence of early resorptions.

Nicholas et al. (1979) exposed female Sprague-Dawley rats to 110 mg/ℓ (110,000 mg/m³) of methyl methacrylate vapor for 17.2 or 54.2 minutes/day during days 6-15 of gestation. The day that vaginal smears were sperm positive was considered day 0 of gestation. Controls consisted of untreated pregnant rats and pregnant rats exposed to filtered air only. The rats were killed on day 20 of gestation. Significantly increased incidence of early fetal death and decreased fetal weight and crown-rump length were observed in the group exposed for 54.2 minutes/day compared with all other groups ($p<0.05$). Exposure for 17.2 minutes/day also caused significant ($p<0.05$) decreases in fetal weight and crown-rump length compared with controls. No effect was observed on resorptions or number of viable fetuses. Hematomas were observed in 7.9% of long-exposure fetuses, 3.9% of short-exposure fetuses, 0.7% of air controls and 1.3% of untreated controls; the incidence in the long-exposure group was significantly greater ($p<0.05$) than both

control groups. Short crooked tails (2%) were seen in fetuses from dams exposed for 54.2 minutes; no crooked tails were found in the other groups. Significantly ($p<0.05$) increased incidences of delayed sternebral ossification was observed in the short-exposure (60.1%) and long-exposure (94.6%) groups compared with air controls (19.8%) and untreated controls (17.5%). The incidence of delayed vertebral ossification was significantly ($p<0.05$) increased in the long-exposure group compared with all other groups. Other skeletal anomalies observed in the long-exposure group but not in any other group included fused ribs, stunted ribs and other vertebral abnormalities. Dose-related increased incidences of rudimentary 14th ribs were seen in both short and long-exposure groups, but the differences were not significantly different compared with controls. Dose-related significant decreases in maternal weight gain and food consumption occurred during and after the exposure to methyl methacrylate.

Singh et al. (1972) injected i.p. doses of 0.1328, 0.2656 and 0.4427 mℓ/kg of methyl methacrylate into groups of five pregnant Sprague-Dawley rats on days 5, 10 and 15 of gestation. The day on which vaginal smears were sperm-positive was designated day 0 of gestation. Controls consisted of five untreated pregnant rats and groups of five pregnant rats injected i.p. with 0.8222 mℓ/kg of distilled water, saline or cottonseed oil. No significant differences were found in numbers of corpora lutea, resorptions, dead fetuses or live fetuses. Mean fetal body weight of the methyl methacrylate treated groups was significantly reduced compared with untreated controls ($p<0.01$) but not compared with distilled water, saline or cottonseed oil treated controls. The incidence of gross abnormalities of fetuses were 0/59, 0/36, 1/50 and 1/50 for the untreated, distilled water, saline

and cottonseed oil controls, respectively. The incidence of gross abnormalities in fetuses of the methyl methacrylate treated dams were 1/43 (2.3%) at 0.1328 mℓ/kg, 4/50 (8.0%) at 0.2656 mℓ/kg and 8/48 (16.7%) at 0.4427 mℓ/kg. The incidences of gross abnormalities in the two higher dose groups were significantly ($p<0.05$) higher than in the pooled controls. The most commonly observed gross abnormalities were hemangiomas and twisted hind legs. The individual incidences were not reported. No skeletal abnormalities were observed in methyl methacrylate treated groups.

McLauglin et al. (1978) exposed groups of 14 and 18 pregnant ICR mice by inhalation to methyl methacrylate at concentrations of 0 or 1330 ppm (5445 mg/m³) for 2 hours, 2 times/day on days 6-15 of gestation. Day 1 of gestation was designated as the day on which a vaginal plug was observed. The mice were killed on day 18 of gestation. No significant differences were found in the number of resorptions, number of dead or live fetuses, litter size or abnormal fetuses. The average fetal weight of the treated group was significantly greater than the control group.

As reviewed by TSCA-ITC (1980) groups of 12 pregnant Dutch rabbits were treated i.p. with methyl methacrylate doses of 0.004, 0.04 or 0.4 mℓ/kg/day from days 6-18 of gestation (ICI, Ltd., 1979). Twelve control rabbits received injections of saline. The rabbits were killed on day 29 of gestation. No teratogenic effects were observed. Reduced fetal weight, possible reduced ossification and increased early resorptions were observed at the highest dosage level.

5.4. OTHER REPRODUCTIVE EFFECTS

Increased estrogen secretion by the ovary in rats was reported by Smirnova and Blagodatin (1977). In rats inhaling 54 mg/m³ methyl meth-

acrylate for 1-4 months continuously, increased estrogen secretion apparently increased the follicle-stimulating activity of the pituitary.

Pregnancy complications in female workers exposed to methyl methacrylate have been reported by Frigo et al. (1981). Excessive blood serotonin was observed, increasing contractile activity of the myometrium.

Sexual disorders in women chronically exposed to methyl methacrylate have been reported by Makarov et al. (1984). Decreased sexuality was reported as an early symptom of toxic effects on the nervous and endocrine systems. Similar effects were reported for males (Makarov, 1984).

5.5. CHRONIC TOXICITY

Groups of 25 male and 25 female Wistar rats were given methyl methacrylate in the drinking water for 2 years (Borzelleca et al., 1964). One group was treated at 2000 ppm for the entire 2-year period. Other groups were treated at 6 and 60 ppm for 4 months, after which the concentrations were increased to 7 and 70 ppm, respectively. Untreated controls consisted of 25 rats/sex. Weight gain was depressed at the high dose during weeks 1-3 but returned to normal for the rest of the experiment. The only effect noted was an increased kidney-to-body weight ratio in high-dose females compared with control. Urine and hematologic values were within normal ranges and histopathologic examination of major organs and tissues showed no treatment-related abnormalities or lesions.

Motoc et al. (1971) treated 50 white rats orally with methyl methacrylate at 25 mg/rat, 2 days/week for 3, 5 or 8 months. The total doses administered were 2750 mg/kg, 5500 mg/kg and 8125 mg/kg, respectively, or 114.6 mg/kg/day. Ulcerations of the glandular epithelium of the stomach were observed and became more severe with duration of treatment. Marked dystrophic and necrotic lesions in the liver were irreversible as treatment

continued. Reversible lesions in the glomeruli were observed in the kidneys. As reviewed by TSCA-ITC (1980), Trecn et al. (1949) found little toxic effect of methyl methacrylate in an oral study using rabbits (23 mg/kg, 24 doses administered within 33 days). Additional details were not provided. In rabbits administered methyl methacrylate orally for 8 months, Shitskova et al. (1977) found liver biochemistry altered, hepatotoxic effects and kidney injury. Further details were not given in the abstract of this Russian study.

Borzelleca et al. (1964) administered methyl methacrylate dissolved in corn oil and incorporated into gelatin capsules to groups of two beagle dogs/sex for 2 years at doses equivalent to dietary levels of 0, 10, 100 and 1000 ppm; at 5 weeks, the 1000 ppm dose was raised to 1200 ppm, at 7 weeks it was raised to 1400 ppm and at 9 weeks to 1500 ppm and remained at this level for the rest of the study (the TWA concentration of the high exposure level was 1473 ppm). The only effect observed was slightly decreased weight gain throughout the study in high-dose animals compared with controls. Spleen-to-body weight ratios were significantly lower in dogs at the 100 ppm (409 mg/m^3) level. Since spleen-to-body weight ratios were not different in the high-dose groups, the toxicologic significance of this finding is questionable. Urine and hematological parameters were normal, as were histopathologic findings.

Groups of 70 male and 70 female Fischer rats were exposed by inhalation to methyl methacrylate at concentrations of 0, 25, 100 and 400 ppm (0, 102, 409 and 11638 mg/m^3) 6 hours/day, 5 days/week for 104 weeks (Hazelton Laboratories America, Inc., 1979b). The only treatment-related histologic change was a slightly increased incidence of mild rhinitis. The lesion was

characterized by a serous to purulent exudate and distended submucosal glands. It was not specified in the review of this study by TSCA-ITC (1980) at which concentration(s) the lesion occurred.

Groups of 25 male Sprague-Dawley rats were exposed by inhalation to methyl methacrylate at concentrations of 0 and 116 ppm (475 mg/m³) methyl methacrylate vapor for 8 hours/day, 5 days/week for 3 months or 6 months. (Tansy et al., 1976, 1980a). In treated rats, mean whole body weights and fat content (at 3 and 6 months) and mean wet lung and spleen weight (at 3 months) were significantly lower compared with controls. A variety of clinical chemistry parameters were significantly increased after 3 or 6 months but were considered toxicologically insignificant because many values were within normal limits. Upon gross and histologic examination, no remarkable changes in the heart, kidneys, spleen, stomach, small intestine or adrenals were observed after 3 or 6 months. Small areas of focal hemorrhage were observed in trachael mucosa after 6 months of exposure. Evidence of liver damage (occasional small focal necrosis, changes in cytoplasmic texture, cell swelling and loss of definition) was observed in rats exposed for 3 or 6 months, but these changes were also seen occasionally in controls. Rats exposed for 6 months also had significantly decreased average small intestinal transit performance (Tansy et al., 1976).

Tansy et al. (1980b) exposed 23 male Sprague-Dawley rats to 116 ppm (475 mg/m³) methyl methacrylate vapor for 7 hours/day, 5 days/week for 3 months. An equal number of control rats were exposed to air. At autopsy, final mean adrenal weight, body weight, epididymal fat pad and popliteal fat pad weights were not significantly different from control values. Exposed animals demonstrated significant decreases in serum bilirubin and increases

in total serum cholesterol. Histological examination was performed on the heart, lung, kidney, small intestine and liver, with "possible presence of liver damage" as the only effect noted.

Motoc et al. (1971) exposed 50 white rats by inhalation to methyl methacrylate at a concentration of 1 mL/84 L of air (~12 ppm or 49 mg/m³) at 20 exposures in 3 months, 41 exposures in 5 months and 63 exposures in 8 months. The duration of each exposure was not reported. Histologic changes in the lungs included interstitial infiltrates, thickening of the septa and marked alveolar desquamation. Lesions in the liver and kidney were less severe and more often reversible than those observed after oral treatment.

In a 42-day inhalation study, Blanchet et al. (1982) used exposed groups of four female Sprague-Dawley rats to vaporized methyl methacrylate at a concentration of 7.6 vol% (76,000 ppm=311,149 mg/m³) for 20 minutes/day for 21 or 42 days. Controls consisted of four animals not exposed to methyl methacrylate. Systolic blood pressure, heart rate, respiration and ECG were monitored on the first day of exposure and on the 21st and 42nd day. During the first exposure, marked changes in respiration and ECG changes were seen. Continued exposure resulted in an initial decrease followed by an increased systolic blood pressure with an increased respiratory and heart rate. At the final testing period, all animals showed abnormal respiratory patterns, ECG changes and demonstrated a heart block pattern, with an increase in systolic blood pressure.

Groups of 56 male and 56 female golden hamsters were exposed by inhalation to methyl methacrylate at 0, 25, 100 and 400 ppm (0, 102, 409, and 1638 mg/m³), 6 hours/day, 5 days/week for 78 weeks (Hazelton Laboratories America, Inc., 1979a). No treatment-related effects were reported.

Blagodatin et al. (1970) presented a report on 152 workers exposed to 2-200 mg/m³ (0.5-50 ppm) methyl methacrylate. Headaches (119), pain in extremities (45), excessive fatigue (32), sleep disturbance (32), loss of memory (30) and irritability (25) were reported. Most of these workers had been employed for ≥10 years.

Cromer and Kronoveter (1976) reported a study of 91 exposed and 43 non-exposed workers in plants manufacturing polymethyl methacrylate sheets. Exposure ranged from 161-200 mg/m³ (4-49 ppm) methyl methacrylate based on a mean 8-hour TWA exposure. No signs or symptoms of toxicity were observed.

Seppalainen and Rajaniemi (1984) studied nerve conduction velocities in 20 dental technicians who handled methyl methacrylate daily. Mild axonal degeneration in areas of the hand with the closest and most frequent methyl methacrylate contact was noted, as evidenced by slower distal sensory conduction velocities. Of the dental technicians, 25% complained of neurological problems in their hands. Allergic responses to methyl methacrylate have been reported after direct skin contact in humans (Fisher, 1954; Pegum and Medhurst, 1971; Shellow, 1954; Spealman et al., 1945). Hypersensitivity to methyl methacrylate was found in 10% of technicians after 2-14 years of contact (Spiechowicz, 1971).

Monroe et al. (1981) studied respiratory health in 780 workers in a plant manufacturing methyl methacrylate. The mean age was 43.5 years and length of service was 17.3 years. Chronic bronchitis was observed in 14% of men and 3% of women (who also smoked less). Men who smoked had the highest incidence (24%). Nonsmokers who worked with methyl methacrylate had low FEV_1 ($p<0.005$) but no other pulmonary function abnormalities were seen. Length of employment was not associated with respiratory abnormalities when effects of cigarette smoking were considered.

Della Torre et al. (1982) reported a clinical study performed on 18 workers employed for an average of 12 years in a factory manufacturing polymethyl methacrylate sheet. Two divisions were made in the group, those exposed to amounts less than the TLV (410 mg/m^3) and those exposed to levels above the TLV. Both groups exhibited nervous disorders and slight mucosal irritation. No changes were noted in liver, cardiovascular and peripheral nervous systems.

In abstracts of studies from the Russian literature, occupational exposure to methyl methacrylate has been associated with cardiovascular disorders (Dorofeeva, 1974; Dorofeeva et al., 1978), hormone imbalance, altered metabolic functions and obesity (Makarov, 1980; Makarov et al., 1980, 1981a,b; Makarov and Makarenko, 1983).

5.6. OTHER RELEVANT INFORMATION

Acute exposure to methyl methacrylate results in prostration and narcosis, with death in 24 hours. LD_{50} values are listed in Table 5-3.

Mallory et al. (1973) investigated the effects of methyl methacrylate on Swiss mice. Groups of 20 mice were treated with methyl methacrylate monomer diluted with olive oil. Controls received only olive oil and another group received chloroform as a positive control for liver damage. Doses ranging from 1-20% methyl methacrylate in 0.1 cc were administered esophageally, and the mice were sacrificed 72 hours later. In the dose ranges from 6-20% methyl methacrylate, minimal liver injury was observed in increasing numbers of mice as the dosage increased. Liver cells were swollen, nuclei altered in size and shape and sinusoids were congested. At a concentration of 11%, 50% of the mice had central and mid-zonal fatty changes with central lobular alteration. At 15-20% methyl methacrylate concentrations, massive fatty infiltration with alteration and disruption of nuclei was observed in 70% of the animals.

TABLE 5-3

LD_{50} and LC_{50} Values for Methyl Methacrylate

Species	Route	LD_{50} or LC_{50}	Reference
Rat	oral	8000 mg/kg	Litchfield, 1978
Rat	oral	7.8 g/kg bw	Deichmann, 1941
Rat	oral	10.0 mℓ/kg	Spealman et al., 1945
Rat	oral	>8.0-<16.0 mℓ/kg	Lawrence et al., 1974
Dog	oral	5.0 mℓ/kg	Spealman et al., 1945
Mice	oral	5.61 mℓ/kg	Lawrence et al., 1974
Mice	oral	51.97 mmol/kg	Tanii and Hashimoto, 1982
Mice	oral	5.5 mℓ/kg	Schwach and Hofer, 1978
Guinea pig	oral	6.3 mℓ/kg	Spealman et al., 1945
Rabbit	oral	6.6 g/kg bw	Deichmann, 1941
Rabbit	oral	6000 mg/kg	Litchfield, 1978
Rat	inhalation	19 mg/ℓ for 8 hours (survived 14.3 mg/ℓ)	Deichmann, 1941
Rat	inhalation	7093 ppm (29,045 mg/m³) for 4-hour exposure	Tansy et al., 1980c
Mice	inhalation	164.22 mg/ℓ for 26.95 minutes	Lawrence and Autian, 1972
Mice	inhalation	55 mg/ℓ for 3 hours	Deichmann, 1941
Mice	inhalation	115.03 mg/ℓ for 55.82 minutes	Lawrence et al., 1974

TABLE 5-3 (cont.)

Species	Route	LD_{50} or LC_{50}	Reference
Mice	inhalation	13.1 mg/ℓ for 2 hours	Karpov, 1954
Rabbit	inhalation	19 mg/ℓ for 8 hours (survived 14.3 mg/ℓ)	Deichmann, 1941
Guinea pig	inhalation	19 mg/ℓ for 8 hours (survived 14.3 mg/ℓ)	Deichmann, 1941
Rat	i.p.	2.8 mℓ/kg	Lawrence et al., 1974
Mice	i.p.	1.20 mℓ/kg	Lawrence et al., 1974
Mice	i.p.	1.13 g/kg bw	Autian, 1975
Mice	s.c.	6.36 g/kg	Castellino and Colicchio, 1969
Rabbit	s.c.	7.68 g/kg	Castellino and Colicchio, 1969
Rabbit	percutaneous	8 mℓ/kg	Lawrence et al., 1974

Mice exposed to 100 ppm (409 mg/m³) and 400 ppm (1638 mg/m³) for a total of 160 hours (6.6 days) exhibited liver enzyme effects (Tansy et al., 1980a) and rats exposed to 1000 ppm for 56 hours showed frank lung damage. Dogs exposed by inhalation to 11,400 ppm (46,682 mg/m³) for 0.5 hour/day for 15 days or 1400 ppm (5733 mg/m³)for 1.5 hours/day for 8 days exhibited liver and kidney degeneration, followed by death (Spealman et al., 1945). Similar studies by these authors produced liver degeneration and death in guinea pigs at levels of 15,900 ppm (65,108 mg/m³) 3 hours/day for 3 days; however, no deaths occurred at concentrations of 9500 ppm, 3 hours/day for 3 days.

In a short-term experiment, McLaughlin et al. (1979) exposed eight female ICR mice to 1500 ppm methyl methacrylate for 2 hours/day for 10 days. Histologic examination of lungs, liver, heart and kidney showed no evidence of damage. Six control mice under similar conditions but not administered methyl methacrylate also showed no evidence of histologic damage.

Holland et al. (1973) injected three dogs by the portal vein, three dogs by the carotid artery and three dogs by the thoracic aorta with 0.05 mL/kg of methyl methacrylate (this dosage consistently produced a transient systemic hypotension and pulmonary damage). Each dog received three injections at 30-minute intervals. Animals were sacrificed 30 minutes after the third injection and tissues were preserved for histologic examination. All nine dogs exhibited vascular congestion, focal hemorrhage and edema in the lungs and random focal congestion and necrosis in the liver. Three of the dogs had glomerular damage in the kidney. No histologic changes were noted in the brain, heart, GI tract or spleen. Blood pressure fell rapidly after introduction of methacrylate.

The effects of methyl methacrylate in acute cardiovascular toxicity appear to be mediated by a cholinergic activity and are involved with calcium availability (Baran, 1983). Calcium infusion reversed all methyl methacrylate induced cardiovascular alterations ($p<0.05$), but cardiac rate remained depressed in dogs administered a bolus (62.4 mg/kg/10 minutes) of methyl methacrylate.

McLaughlin et al. (1973) administered 10 mg/kg bw methyl methacrylate i.v. to five beagle dogs. No statistically significant changes in hematocrit or arterial PO_2, PCO_2 or pH were observed, and no gross abnormalities occurred. In seven dogs that received successive doses of 25, 50 and 75 mg/kg bw, statistically significant changes ($p=0.01$) occurred after doses of 75 mg/kg bw. A decrease in pH and arterial PO_2 and an increase in arterial PCO_2, base deficit and hematocrit were observed. Clinical signs of pulmonary edema (serosanguineous secretions in the endotracheal tube) developed in most dogs after administration of the last dose. At autopsy, lungs of all dogs showed hemorrhagic areas as large as 2 cm in diameter. On histological examination, clumped birefringent crystalline material was found adjacent to small terminal bronchioles and scattered randomly in interalveolar septa, with the amount present a function of dosage. Some lungs showed pulmonary edema. No consistent changes were seen in the liver and spleen, but occasional mild fatty metamorphosis of the liver and varying amounts of splenic congestion were observed.

Fairman et al. (1984) investigated pulmonary hypertension and increases in lung vascular permeability in sheep given a bolus of 12 mg/kg of methyl methacrylate, intravenously. These authors concluded that methyl methacrylate in sheep causes dose-dependent increased pulmonary microvascular

permeability without polymorphonuclear trapping in the pulmonary parenchyma, with transient pulmonary hypertension occurring after high methyl methacrylate doses.

Bright et al. (1972) infused methyl methacrylate into 10 animals (6 sheep, 3 dogs, 1 chimpanzee) in doses from 1-200 mg/100 mℓ blood. At levels up to 5 mg/100 mℓ, no changes were observed. From 10-50 mg/mℓ hypotension with depressed cardiac contractility and increased venous pressure occurred. Blood pressure returned to normal in 10 mintues. Gross pathological changes observed were focal pulmonary and epicardial hemorrhages, with focal pulmonary vascular congestion with fluid-filled alveoli. Dose levels >50 mg/mℓ caused death.

Schuh et al. (1973) found alterations of arterial pressure or heart rate in 52 total hip joint replacement patients who had intraosseous application of methyl methacrylate. Phillips et al. (1971) also reported a drop in blood pressure.

Cavelier et al. (1981) reported allergic sensitization to methyl methacrylate in humans; Jennette et al. (1982) found it to be nonimmunogenic in rabbits. Occupational hazards from use of methyl methacrylate in orthopedic surgery have been reviewed by Fregert (1983) and include the following: allergic contact hand eczema in dentists and dental technicians; sore mouth in patients with dentures (Fisher, 1954; Shellow, 1954); allergic contact eczema in orthopedic surgeons caused by penetration of gloves with methyl methacrylate (Pegum and Medhurst, 1971); headache and irritation of the eyes and respiratory tract from vapors during surgery. Adverse effects of methyl methacrylate have been noted in bone metabolism (Pedersen et al., 1983), on circulation, causing a drop in blood pressure and cardiovascular changes

(Schuh et al., 1973; Mir et al., 1973, 1974; Blanchet et al., 1982) that are due to direct toxic effect on the myocardium (Milanesi et al., 1982) and on renal function (Miller et al., 1982).

Incubation of mouse L cells with a concentration of 3.2×10^{-2} M methyl methacrylate suppressed cell division. DNA synthesis was inhibited after 12 hours and protein synthesis after 24 hours (Schmalz, 1979).

Welch (1978) found that a concentration of 0.5% methyl methacrylate monomer reduced the ability of macrophages in vitro to phagocytose cultures of Staphylococcus epidermidis. When mice were injected with 0.03 mℓ, capacity of peritoneal macrophages to phagocytose bacteria was reduced. This concentration was also sufficient to alter morphology and viability of blood cells and tissue cells in culture, polymorphonuclear cells being damaged to the greatest extent. These effects may be responsible for tissue damage following total joint arthroplastic surgery.

In studies of 99% chemically pure methyl methacrylate and the liquid component of prosthetic acrylic material, Danilewicz-Stysiak (1980) used concentrations of 3.5, 3, 2.5, 2, 1.5, 1, 0.01, 0.0075, 0.005 and 0.0025 mg/mℓ on fibroblast cultures from chicken embryo heart. Concentrations from 1.5-3.5 mg/mℓ totally inhibited growth and killed the cultures. Because of additional substances that had cytotoxic activity, the toxicity threshold for the monomer was 0.01 mg/mℓ and for the liquid solution was 0.0025 mg/mℓ.

Turkish and Galin (1980) used tissue cultures of secondary rabbit kidney cells and concentrations of methyl methacrylate ranging from 0.05-5%. No pathologic changes were observed at concentrations of $\leq$0.1%. Methyl methacrylate is used in contact lenses; these authors concluded that data from previous studies on rate of elution of monomer from polymethylmethacrylate

and from published studies of aqueous humor dynamics (combined with their study) indicated that the monomer level in intraocular lenses would be less than the concentration found to be toxic to living cells in tissue culture.

Verkkala et al. (1983) exposed the tail skin of rats to liquid methyl methacrylate for 3 hours/day for 8 weeks. A local neurotoxic reaction occurred, with abnormal muscle responses when rat tail motor nerves were stimulated by a skin electrode after 4 weeks of exposure. Keratolysis also was noted, and subdermal structures were affected.

Wynkoop et al. (1982) measured systemic activities of neuroactive substances after s.c. injection of 200 µℓ methyl methacrylate into Sprague-Dawley rats. Twenty-one rats were exposed to methyl methacrylate, with another 21 used for control levels. Seven fasted rats from each group were sacrificed at 3, 7, and 14 days. Elevated levels of epinephrine and norepinephrine were seen, but only norepinephrine levels were significantly different from controls.

Rats exposed to 400 ppm (1784 mg/m^3) methyl methacrylate in air for 60 minutes showed depression of multiple-unit electrical activity in the lateral hypothalamus and ventral hippocampus (Innes and Tansy, 1981).

Boehling et al. (1977) found that monomeric methyl methacrylate acts on the desheathed myelinated nerve and on the node of Ranvier, decreasing the amplitude in amphibian sciatic nerve; the effects were found to be dose dependent.

Chemically induced microvascular changes were studied in the hamster cheek pouch using Simplex-P, which contains methyl methacrylate. Severe microcirculatory changes were seen with extensive intravascular hemolysis and circulatory standstill, resulting in necrosis (Linder and Romanus, 1976). Linder (1976) investigated the reaction of rabbit ear tissue to

methyl methacrylate. In all cases, bleeding and tissue necrosis through the entire thickness of the ear occurred at the distal injection sites. At the proximal injection sites, the skin of the inner surface of the ear was intact. This study confirmed that methyl methacrylate is highly toxic to tissues in direct contact with this substance.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethal effects of methyl methacrylate were determined in fathead minnows, Pimephales promelas, bluegill sunfish, Lepomis macrochirus, goldfish, Carassius auratus and guppies, Poecilia reticulata (Pickering and Henderson, 1966). Duplicate 96-hour tests in fatheads were conducted in hard (360 mg $CaCO_3$/ℓ) and soft (20 mg $CaCO_3$/ℓ) water while other species were tested only in soft water. The 24-, 48- and 96-hour LC_{50} values for fatheads exposed to soft water were 421-455, 338-455 and 159-160 mg methyl methacrylate/ℓ, respectively. In hard water, 24-, 48- and 96-hour LC_{50} values were 392-499, 338-368 and 311-320 mg/ℓ, respectively, for fatheads. The 24-, 48- and 96-hour LC_{50} values in bluegill sunfish were 368, 358, and 232 mg methyl methacrylate/ℓ, respectively. In goldfish, a LC_{50} value of 423 mg/ℓ was reported for 24- and 48-hour exposures and 277 mg/ℓ was the 96-hour LC_{50}. The LC_{50} value of 368 mg methyl methacrylate/ℓ was determined for guppies exposed for 24, 48 and 96 hours (Pickering and Henderson, 1966).

In acute toxicity tests using the golden orfe, Leuciscus idus melanotus, 48-hour LC_0, LC_{50} and LC_{100} values were 320, 350 and 380 mg methyl methyacrylate/ℓ, respectively (Juhnke and Luedemann, 1978).

In the water flea, Daphnia magna, 24-hour toxicity tests were conducted to establish concentrations of methyl methacrylate causing immobilization (Bringmann and Kuehn, 1982). The 24-hour EC_0, EC_{50} and EC_{100} values were 502, 720 and 1042 mg/ℓ, respectively.

6.2. CHRONIC EFFECTS

Pertinent data regarding the toxic effects of chronic exposure to methyl methacrylate on aquatic species were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Bringmann and Kuehn (1978) determined the toxicity threshold level of methyl methacrylate causing inhibited cell multiplication in a blue-green algae, Microcystis aeruginosa and a green algae, Scenedesmus quadricauda. Levels at 120 and 37 mg/ℓ caused the first detectable reduction in cell multiplication (determined turbidimetrically) in the blue-green and green algae, respectively, following 8 days of exposure.

6.4. RESIDUE

Pertinent data regarding the residue of methyl methacrylate in aquatic organisms or the aquatic environment were not located in the available literature as cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Bringmann and Keuhn (1980) reported toxicity threshold levels for inhibited cell multiplication at 100 and 450 mg methyl methacrylate/ℓ in bacteria, Pseudomonas putida and protozoa, Entosiphon sulcatum. Test cultures of bacteria and protozoa were exposed for 16 and 72 hours, respectively.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

OSHA reported a TWA of 410 mg/m³ (100 ppm) (Code of Federal Regulations, 1981). ACGIH (1984) listed the same level [410 mg/m³ (100 ppm)] and a STEL of 510 mg/m³ (125 ppm). These levels were considered to be protective against the irritating effects and acute systemic effects (ACGIH, 1980). It was cautioned that information was insufficient to determine if the levels were protective against effects of chronic exposure.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of methyl methacrylate were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

No evidence of carcinogenicity of methyl methacrylate was observed in rats exposed at drinking water concentrations ≤2000 ppm for 2 years (Borzelleca et al., 1964) or in hamsters or rats exposed by inhalation at concentrations ≤400 ppm (≤1638 mg/m³), 6 hours/day, 5 days/week for 18 months (hamsters) or 2 years (rats) (Hazelton Laboratories America, Inc., 1979a,b). No local tumors were found in rats that were painted with methyl methacrylate on the back of the neck 3 times/week for 4 months (Oppenheimer et al., 1955). Singh et al. (1972) observed increased incidences of hemangiomas in fetuses from female rats treated i.p. with methyl methacrylate at doses of 0.1328, 0.2656 or 0.4427 mℓ/kg (~125, 250 or 416 mg/kg, using the density of methyl methacrylate of 0.939 g/mℓ given in Section 1.2.) during gestation. A causal relationship for increased incidences of cancer of the colon and rectum from occupational exposure to ethyl acrylate/methyl methacrylate was suggested in a retrospective epidemiology study (see Table 5-1); however, the causal relationship could not be established when relative accumulated total exposures and latency were considered (Rohm and Haas Co., 1984). Moreover, exposure to ethyl acrylate and methyl methacrylate could not be separated. Further analyses and studies are being conducted (Rohm and Haas Co., 1984). Histopathologic examinations of tissue from rats and mice in a chronic inhalation study are in progress (NTP, 1985).

Methyl methacrylate was negative for reverse mutations in five strains of Salmonella typhimurium with and without metabolic activation when tested by plate incorporation, liquid preincubation or vapor phase techniques (Barsky, 1975; Anderson 1976a; Lijinsky and Andrews, 1980; Waegemaekers and Bensink, 1984; Ishidate et al., 1981). Negative results were also obtained

in the micronucleus test and the dominant lethal assay in mice (Hacmiya et al., 1982; Anderson, 1976a). Methyl methacrylate was positive in a forward mutation assay in S. typhimurium strain TM677 with activation (Poss et al., 1979); in tests for chromosomal aberrations in rats treated in vivo (Anderson, 1976b); and in cultured hamsters fibroblasts (Ishidate et al., 1981).

Inhalation exposure of pregnant rats to methyl methacrylate resulted in an increased number of early resorptions at exposures of 1000 ppm (4094 mg/m³), 5 hours/day on days 6-15 of gestation (Hodge and Palmer, 1977). Nicholas et al. (1979) found delayed ossification, decreased fetal crown-rump length and decreased fetal body weight in the offspring of rats exposed to 110 mg/ℓ (110,000 mg/m³) for 17.2 and 54.2 minutes/day on days 6-15 of gestation. At the longer exposure, there were also increased incidences of hematomas, crooked tails and skeletal anomalies. Dose-related decreased body weight gain was observed in the dams. The only observed effect of inhalation exposure of pregnant mice to methyl methacrylate at 5445 mg/m³, 4 hours/day on days 6-15 of gestation was increased fetal body weight (McLaughlin et al., 1978). Dose-related increased incidences of gross abnormalities (hemangiomas and twisted hind legs) were observed in fetuses of rat dams treated i.p. at 125, 250 and 415 mg/kg/day on days 5, 10 and 15 of gestation (Singh et al., 1972). Reduced fetal weight, reduced ossification and increased early resorptions were observed in the fetuses of rabbits treated i.p. with 0.4 mℓ/kg/day (376 mg/kg/day, using the density of 0.939 g/mℓ as given in Section 1.2.) on days 6-18 of gestation (ICI, Ltd., 1979). No effects were observed at 0.04 or 0.004 mℓ/kg/day (37.6 or 3.76 mg/kg/day).

The only effect observed in rats treated with methyl methacrylate in the drinking water at 0, 6-7, 60-70 or 2000 ppm (0, 0.75, 7.54 and 179 mg/kg/day for females and 0, 0.55, 5.39 and 133 mg/kg/day for males) was an increased kidney-to-body weight ratio in females at the highest dose (Borzelleca et al., 1964). Motoc et al. (1971) found ulceration of the stomach, irreversible dystrophic and necrotic lesions in the liver and unspecified changes in the glomeruli of the kidney in rats treated orally with 25 mg/rat, 2 days/week for 3, 5 or 8 months. The total doses administered were 2750 mg/kg, 5500 mg/kg and 8125 mg/kg, respectively, or ~115 mg/kg/day. In dogs treated orally with methyl methacrylate in gelatine capsules at equivalent dietary levels of 0, 10, 100 and 1473 (TWA) ppm (0, 0.4, 4 and 58 mg/kg/day, assuming that a dog consumes a daily amount of food equal to 4% of its body weight) for 2 years, the only observed treatment-related effect was a slight but nonsignificant decrease in body weight of the high-dose dogs (Borzelleca et al., 1964).

Several chronic and subchronic inhalation studies have been conducted with methyl methacrylate. Rats exposed to concentrations of 102, 409 and 1638 mg/m^3, 6 hours/day, 5 days/week for 2 years had very slight increased incidences of mild rhinitis, while no effects were observed in hamsters exposed to the same concentrations for 18 months (Hazelton Laboratories America, Inc., 1979a,b). Rats exposed to 475 mg/m^3 for 7 or 8 hours/day, 5 days/week for 3 or 6 months had decreased body weight gain, decreased lung and spleen weights, tracheal hemorrhage, liver damage (focal necrosis, changes in cytoplasmic texture, cell swelling and loss of definition) and decreased intestinal transit performance, decreased serum bilirubin and increased serum cholesterol (Tansy et al., 1976, 1980a,b). Exposure of rats

to methyl methacrylate at a concentration of 7.6 % vol. (76,000 ppm=311,149 mg/m³) for 20 minutes/day for 42 days resulted in systolic blood pressure changes, increased respiratory and heart rates and ECG changes indicative of heart block (Blanchet et al., 1982).

Occupational exposure to methyl methacrylate has been associated with several disorders including axonal degeneration in the hands of dental technicians (Seppalainen and Rajaniemi, 1984), allergy after direct skin contact (Fisher, 1954; Pegum and Medhurst, 1971; Spiechowicz, 1971), nervous disorders and mucosal irritation in workers exposed at ~410 mg/m³ (Della Torre et al., 1982), cardiovascular disorders (Dorofeeva et al., 1978), hormone imbalance, altered metabolic functions and obesity (Makarov, 1980; Makarov et al., 1980, 1981a,b; Makarov and Makarenko, 1983). In a study from the Russian literature, headaches, pain in extremities, fatigue, loss of memory and irritability were common complaints of workers exposed to 2-200 mg/m³ (Blagodatin et al., 1970); however, Cromer and Kronoveter (1976) found that workers exposed to 161-200 mg/m³ had no symptoms or signs of toxicity.

The available data suggest that methyl methacrylate is not carcinogenic to rats exposed by drinking water (Borzelleca et al., 1964) or to rats and hamsters exposed by inhalation (Hazleton Laboratories America, Inc., 1979a,b); results from an inhalation bioassay in mice and rats are forthcoming (NTP, 1985). A causal relationship between occupational exposure to methyl methacrylate and carcinogenesis in humans is yet to be established (Rohm and Haas Co., 1984). Therefore, it is appropriate to derive a tentative ADI for methyl methacrylate based on toxicity data. Although toxic effects from chronic and subchronic inhalation exposure of animals have been found, the ADI is more appropriately derived from oral exposure data.

Borzelleca et al. (1964) found that rats exposed to methyl methacrylate in the drinking water at 2000 ppm had increased kidney-to-body weight ratios, but found no histopathologic changes in the major organs and tissues, including the kidneys, liver and GI tract at this exposure level or at the next lowest level of 60 ppm for 5 weeks, followed by 70 ppm for 8 weeks. TWAs were calculated based on body weight data provided by the authors. The TWA weights are estimated as follows:

Females	control	279 g
	low-dose	317 g
	mid-dose	307 g
	high-dose	282 g
Males	control	479 g
	low-dose	469 g
	mid-dose	475 g
	high-dose	470 g

Unfortunately the authors presented only mean fluid consumption values and it is not clear if these values represent weighted averages. Using the provided fluid consumption data and TWA body weight values the following mg/kg/day doses are estimated. For the low- and mid-dose groups the water concentrations were increased after 4 weeks from 6-7 ppm and from 60-70 ppm, respectively. The high-dose group received 2000 ppm for the entire study duration.

Females	low-dose (6-7 ppm):	0.753 mg/kg/day
	mid-dose (60-70 ppm)	7.54 mg/kg/day
	high-dose (2000 ppm):	179 mg/kg/day
Males	low-dose (6-7 ppm):	0.55 mg/kg/day
	mid-dose (60-70 ppm):	5.39 mg/kg/day
	high-dose (2000 ppm):	133 mg/kg/day

Motoc et al. (1971) found dystrophic and necrotic lesions in liver, unspecified kidney lesions and stomach ulcers in rats treated orally by

gavage 2 times/week with doses ~115 mg/kg for 3, 5 or 8 months. The lesions became more severe as treatment continued. These data suggest that a bolus dose administered by gavage may be more toxic than an equivalent intermittant daily exposure by drinking water. Chronic exposure of rats to methyl methacrylate in drinking water more closely reflects chronic exposure of humans to methyl methacrylate than does the bolus treatment of 25 mg/rat, 2 days/week. In addition, the Motoc et al. (1971) study utilized only 1 dose and incompletely reported the experimental protocol.

Borzelleca et al. (1964) also treated dogs with methyl methacrylate dissolved in corn oil in gelatine capsules at equivalent dietary concentrations of 0, 10, 100 and 1473 ppm. Using estimated TWA body weights and assuming dogs consume 4% of their body weight/day (the authors did not provide food consumption data) these feeding levels correspond to 0, 0.4, 4 and 58 mg/kg/day. This study was of 2 years duration which would be considered subchronic in the dog. The only effect was a slightly, but not significantly, decreased body weight of the dogs in the high-dose group. Motoc et al. (1971) identified an effect level in the rat of ~115 mg/kg when this dose was administered by gavage 2 days/week for 8 months

The only chronic oral study available is that of Borzelleca et al. (1964) in which rats were exposed to methyl methacrylate by their drinking water for 2 years. A LOAEL in females corresponding to ~179 mg/kg/day was reported based on increased kidney-to-body weight ratios and a NOEL for males of ~133 mg/kg/day (highest dose tested). The next exposure level, ~7.5 and 5.4 mg/kg/day for females and males, respectively, represented NOELs for males is not considered appropriate for ADI derivation because of the gavage data which showed effects at lower doses. Although the drinking water studies are in general more appropriate to human exposure situations,

since the factors involved in the toxicity differential are incompletely characterized and since the ADI should be designed to be protective for a variety of exposure conditions, it is felt that the gavage data cannot be ignored. With this in mind, the highest NOEL from a chronic study, which is below an effect level is the estimated dose of 7.5 mg/kg/day in female rats. Dividing by an uncertainty factor of 100 (10 for interspecies extrapolation, and 10 for interindividual variability) and multiplying by 70 kg results in an ADI of 5.3 mg/day. This ADI should also be protective against teratogenic, fetotoxic and embryotoxic effects of methyl methacrylate based upon estimated doses from inhalation studies. However, oral teratology studies were not located.

Methyl methacrylate has been shown to cause fetotoxic, embryotoxic or teratogenic effects in rats during gestation at inhalation exposures of 4094 mg/m^3, 5 hours/day (Hodge and Palmer, 1977) and 110,000 mg/m^3 for 17.2 and 54.2 minutes/day (Nicholas et al. 1979). By expanding these exposures over 24 hours and multyplying by the inhalation rate of a rat (0.223 m^3/day), by the absorption coefficient of 0.5 and dividing by the average weight of a rat (0.35 kg), equivalent doses in mg/kg/day can be calculated. Thus, 4094 mg/m^3, 5 hours/day is equivalent to 272 mg/kg/day, and 110,000 mg/m^3 for 17.2 minutes/day (0.29 hours/day) is equivalent to 423 mg/kg/day. Intraperitoneal administration during gestation of doses $\geq$125 mg/kg/day in rats (Singh et al., 1972) and 376 mg/kg/day in rabbits (ICI, Ltd., 1979) also resulted in teratogenic and fetotoxic effects. Clearly, the NOAEL of 42.7 mg/kg/day for chronic exposure is much lower than these i.p. doses and the equivalent doses derived from inhalation exposure.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The available chronic and subchronic oral and inhalation studies and teratogenicity studies of methyl methacrylate were discussed in Section 5.3. and 5.5. The study of Borzelleca et al. (1964), in which female rats given drinking water containing 2000 ppm methyl methacrylate (156 mg/kg/day, assuming a rat consumes a daily amount of water equal to 7.8% of its body weight) had an increased kidney-to-body weight ratio in the absence of histopathologic changes, could be used to calculate a CS. Motoc et al. (1971), however, found more severe effects (liver necrosis and unspecified kidney lesions) at a lower daily dosage (~115 mg/kg/day administered 2 times/week for 8 months) in rats. As discussed in Chapter 8, a possible reason that Motoc et al. (1971) found histopathologic lesions in the liver and kidney at 115 mg/kg/day while Borzelleca et al. (1964) found no changes at dosages $\leq$133 mg/kg/day is the difference in toxicity between a bolus gavage dose and intermittent drinking water exposure. The only available chronic oral study (Borzelleca et al., 1964) is the most appropriate choice for estimating a CS. An MED of 1994 mg/day can be derived from the Borzelleca et al. (1964) drinking water study by multiplying the dose of 156 mg/kg/day by the cube root of the ratio of animal body weight (0.28 kg from the study) to the human body weight (assumed to be 70 kg) and by multiplying by 70 kg. The MED corresponds to an RV_d of 1. Increased kidney-to-body weight ratio in the absence of histopathology warrants an RV_e of 4. The product of the RV_d and RV_e is the CS of 4, which corresponds to an RQ of 5000.

CSs can also be calculated from the inhalation studies. Hazelton Laboratories America, Inc. (1979a,b) exposed rats and hamsters to methyl

methacrylate at 102, 409 and 1638 mg/m³ 6 hours/day, 5 days/week for 2 years (rats) or 18 months (hamsters). No effects were observed in hamsters, but rats had increased incidences of milk rhinitis, presumably at all exposure levels. Assuming a rat ventilatory volume of 0.223 m³/day and a rat body weight of 0.35 kg, 102 mg/m³, 6 hours/day for 5 days/week can be converted to an equivalent human MED of 139 mg/day as follows:

$$102 \text{ mg/m}^3 \times 6 \text{ hours} \div 24 \text{ hours} \times 5 \text{ days} \div 7 \text{ days} \times$$
$$0.223 \text{ m}^3\text{/24 hours}, \div 0.35 \text{ kg} \times \sqrt[3]{0.35 \text{ hour}} \times 70.$$

The RV_d corresponding to the MED is 2.3. The highest RV_e that can be assigned to such a mild local nonsystemic effect is 2. The CS is 4.6 and the RQ is 5000.

More severe effects (focal necrosis, texture changes in the cytoplasm and hepatocellular hypertrophy in the liver, focal hemorrhage of the trachea, reduced lung and spleen weights and impaired GI motor functions as evidenced by reduced intestinal transit time) were observed in rats exposed to 475 mg/m³, 8 hours/day, 5 days/week for 6 months (Tansy et al., 1976, 1980a). Using the assumptions for inhalation exposures and expanding from intermittent to continuous exposure, an equivalent human dose of 863 mg/day is obtained. Because of the subchronic nature of the study, the human dose is divided by an uncertainty factor of 10 to give an MED of 86.3 mg/day, with a corresponding RV_d of 2.6. The effects described warrant an RV_e of 7; the CS is 18.2, corresponding to an RQ of 1000.

CSs can also be calculated for the inhalation teratogenicity studies. Hodge and Palmer (1977) found an increased incidence of early resorptions (RV_e=8) in rats exposed at 4094 mg/m³, 5 hours/day on days 6-15 of gestation. The human MED is 6505 mg/day, corresponding to an RV_d of 1. The CS is 8 and the RQ is 1000.

In the study of Nicholas et al. (1979), the longer exposure of 54.2 minutes/day (0.9 hours/day) at 110,000 mg/m³ resulted in gross abnormalities in fetuses (hematomas, crooked tail) and reduced body weight of dams. The human MED is 31,460 mg/day, with an RV_d of 1. Teratogenicity at a dose that causes maternal toxicity warrants an RV_e of 9. The CS is 9 and the RQ is 1000.

As seen from Table 9-1, the highest CS results from the 6-month inhalation study of Tansy et al. (1976, 1980a). Using the MED of 86.3 mg/day, the RV_d of 2.6, the RV_e of 7 and the CS of 18.2, an RQ of 1000 is recommended (Table 9-2).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The available data for the carcinogenicity of methyl methacrylate were presented in Section 5.1. No treatment-related histopathologic lesions were observed in rats treated with methyl methacrylate in the drinking water at $\leq$2000 ppm for 2 years (Borzelleca et al., 1964) or in hamsters or rats exposed by inhalation at concentrations $\leq$400 ppm ($\leq$1638 mg/m³), 6 hours/day, 5 days/week for 18 months (hamsters) or 2 years (rats) (Hazelton Laboratories America, 1979a,b). Methyl methacrylate did not induce local tumors in rats that were painted on the back of the neck, 3 times/week for 4 months and observed throughout their lives (Oppenheimer et al., 1955). Fetuses from rat dams treated i.p. with methyl methacrylate at doses of ~125, 250 and 416 mg/kg/day on days 6-15 of gestation had dose-related increased incidences of gross abnormalities (Singh et al., 1972). Some of these were hemangiosarcomas, but individual incidences were not reported, precluding any conclusions with regard to tumor incidences. The histopathologic studies from an inhalation bioassay of methyl methacrylate are in progress (NTP, 1985). Although a causal relationship for increased

TABLE 9-1

Composite Scores for the Toxicity of Methyl Methacrylate

Route	Species	Dose/Exposure	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	rat	179 mg/kg/day (2000 ppm in drinking water) 2 years	1,994	1	increased kidney-to-body weight ratio	4	4	5000	Borzelleca et al., 1964
Inhalation	rat	102 mg/m³, 6 hours/day, 5 days/week for 2 years	139	2.3	mild rhinitis	2	4.6	5000	Hazelton Laboratories America Inc., 1979b
Inhalation	rat	475 mg/m³ 8 hours/day, 5 days/week for 6 months	86.3*	2.6	liver histopathology, focal hemorrhage of trachea, decreased lung and spleen weight, impaired GI motor performance	7	18.2	1000	Tansy et al. 1976, 1980a
Inhalation	rat	4094 mg/m³ 5 hours/day on days 6-15 of gestation	6,505	1	embryotoxicity: increase early resorptions	8	8	1000	Hodge and Palmer, 1977
Inhalation	rat	110,000 mg/m³, 0.9 hrs/day on day 6-15 of gestation	31,460	1	teratogenicity with maternal toxicity	9	9	1000	Nicholas et al. 1979

*The equivalent dose was divided by an uncertainty factor of 10 to protect for chronic exposure.

TABLE 9-2

Methyl Methacrylate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	86.3 mg/day
Effect:	liver necrosis, hemorrhage of trachea, decreased lung and spleen weights impaired GI motor performance
Reference:	Tansy et al. (1976, 1980a)
RV_d:	2.6
RV_e:	7
Composite Score:	18.2
RQ:	1000

*Equivalent human dose

incidences of colorectal cancer from occupational exposure to ethyl acrylate/methyl methacrylate was suggested by an epidemiology study (see Table 5-1), the causal relationship could not be established when relative total exposures and latencies were considered (Rohm and Haas Co., 1984). Furthermore, exposure to methyl methacrylate could not be separated from exposure to ethyl acrylate. Further analyses and studies are planned (Rohm and Haas Co., 1984).

There is principally negative evidence with inadequate evidence from the i.p. teratology study of Singh et al. (1972) that methyl methacrylate is carcinogenic to animals.

Inadequate evidence for carcinogenicity to humans was provided by the epidemiology study of Rohm and Haas Co. (1984). According to the IARC classification scheme, methyl methacrylate is tentatively placed in Group 3, until further data become available. Based upon the proposed U.S. EPA guidelines for carcinogen risk assessment, methyl methacrylate is classified as a Group D (not classifiable as to human carcinogenicity) compound. This classification is based on inadequate or insufficient evidence of carcinogenicity in acceptable animal studies and in exposed human populations.

10. REFERENCES

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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